Alnylam Reports Updated Positive Results from Phase 1/2 Study of Lumasiran in Patients with Primary Hyperoxaluria Type 1

October 4, 2018

− Lumasiran Treatment Resulted in 75 Percent Mean Maximal Reduction in Urinary Oxalate Relative to Baseline, with 100 Percent of Patients Achieving Levels of Urinary Oxalate Less Than 1.5 Times Upper Limit of Normal –

− Lumasiran Shows Encouraging Safety Profile with a Median of Seven Months and up to 14 Months Study Duration –

− Company Initiates ILLUMINATE-A Phase 3 Study –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 4, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today updated positive results from its Phase 1/2 clinical study of lumasiran, an investigational, subcutaneously administered RNAi therapeutic targeting glycolate oxidase (GO) for the treatment of primary hyperoxaluria type 1 (PH1). Results were presented at the 2018 European Society for Paediatric Nephrology (ESPN) Annual Meeting on October 4 in Antalya, Turkey. The Company also announced the initiation of ILLUMINATE-A, a global Phase 3 pivotal trial of lumasiran in children and adults with PH1. The study will enroll approximately 30 patients and is designed in alignment with FDA with a primary endpoint based on reduction of urinary oxalate at six months. Alnylam expects to report topline results from ILLUMINATE-A in late 2019 and, if positive, submit filings for regulatory approval starting in early 2020.

New results from the Phase 1/2 study were as of a data cut-off date of August 15, 2018. Lumasiran demonstrated a mean maximal reduction in urinary oxalate of 75 percent (range: 43-87 percent) relative to baseline across cohorts dosed at 1 mg/kg monthly or 3 mg/kg monthly or quarterly (N=20). The mean reduction relative to baseline was 66 percent when measured 28 days post last dose. All patients (100 percent) achieved oxalate lowering to less than 1.5 times the upper limit of normal (less than 0.69 mmol/24hr/1.73m^2). Among patients receiving 3 mg/kg monthly or quarterly doses of lumasiran (N=12), 83 percent achieved urinary oxalate levels within the normal range (less than 0.46 mmol/24hr/1.73m^2). Furthermore, lumasiran-treated patients in all cohorts experienced a mean maximal decrease of 76 percent in the ratio of urinary oxalate to creatinine – a corroborative measure of oxalate reduction that addresses the variability that is inherent to 24 hour urine collections.

“We are pleased to present these data that we believe provide a strong foundation for lumasiran as an investigational RNAi therapeutic for the treatment of PH1, a devastating and life-threatening disease caused by overproduction of oxalate that deposits in the kidneys and other tissues. We’re also excited to have now initiated the ILLUMINATE-A Phase 3 pivotal study, which is expected to read out in late 2019, supporting a potential regulatory approval in 2020, if positive,” said Pritesh J. Gandhi, PharmD., Vice President and General Manager, Lumasiran program at Alnylam. “Given the lack of approved treatment options, we believe lumasiran has the potential to address the significant unmet need that PH1 represents.”

“PH1 is an ultra-rare disease characterized by an inevitable and progressive decline in kidney function leading to systemic manifestations and ultimately multi-organ dysfunction. Once the kidneys fail, the only viable therapeutic option is a dual liver/kidney transplant,” said Prof. Pierre Cochat, M.D., Ph.D., Reference Center for Rare Kidney Diseases, Lyon University Hospital, France; President, International Pediatric Nephrology Association (IPNA) and an investigator in the lumasiran study. “Given the profound unmet need in this disease setting, the Phase 1/2 results presented for lumasiran are encouraging, particularly in light of the clinically meaningful effect of lumasiran on lowering urinary oxalate for every patient relative to their baseline and with all patients achieving near normal levels of oxalate.”

The Phase 1/2 safety results in patients with PH1 were based on a median study duration of seven months (range: 5 to 14 months) since first dose. As of the data cut-off date, there were no discontinuations from study treatment. Serious adverse events (SAEs) were reported for one patient (33 percent) receiving placebo and five patients (25 percent) receiving lumasiran; none were related to study drug. The placebo patient experienced acute pyelonephritis and kidney stones. The lumasiran patients with SAEs included one patient with vomiting, one patient with abdominal pain, fever and vomiting, one patient with gastroenteritis, and two patients with kidney stones. Adverse events (AEs) were reported in three (100 percent) patients during placebo dosing and 19 (95 percent) patients after lumasiran dosing. The majority of AEs were mild or moderate in severity and were assessed as unrelated to study drug. Injection site reactions (ISRs) were reported in three (15 percent) patients receiving lumasiran. ISRs were mild or moderate in severity and were self-limiting. Lumasiran was not associated with any clinically significant adverse laboratory findings. In patients receiving lumasiran, plasma glycolate levels increased consistent with the pharmacology of lumasiran and results from healthy volunteers in Part A of the Phase 1/2 study. This increase was not associated with any safety findings.

About the Lumasiran Phase 1/2 Study Part B
The Phase 1/2 Part B study of lumasiran is a randomized (3:1 drug:placebo), single-blind, placebo-controlled evaluation of lumasiran in patients with PH1. In this multi-dose study, patients in Cohorts 1 and 2 received three monthly doses of lumasiran at 1 mg/kg or 3 mg/kg, respectively; Cohort 3 received two quarterly doses at 3 mg/kg. An additional eight patients received open-label lumasiran in expansions of each of the first two cohorts, totaling 20 patients enrolled. Patients randomized to the placebo group also received subsequent subcutaneous administration of lumasiran following administration of placebo. Patients had a mean age of 14.9 years (range: 6-43) and a mean estimated glomerular filtration rate (eGFR) of 77 mL/min /1.73m^2 (range: 42-131).

About the ILLUMINATE-A Phase 3 Study
The ILLUMINATE-A Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately 30 patients with a documented diagnosis of PH1. Patients will be randomized 2:1 to receive three monthly loading doses of lumasiran or placebo at 3 mg/kg followed by quarterly maintenance doses. The primary endpoint is the reduction of urinary oxalate at six months relative to baseline in the patients treated with lumasiran as compared to placebo. Key secondary and exploratory endpoints will evaluate additional measures of urinary oxalate, estimated glomerular filtration rate (eGFR), safety and tolerability, and quality of life. At month 6, the placebo patients will cross over to the lumasiran arm for long-term follow up out to 60 months. For more information on ILLUMINATE-A (NCT03681184) please visit

clinicaltrials.gov, email clinicaltrials@alnylam.com or call 877-256-9526 in North America and +31 20 369 7861 in Europe.

About Lumasiran
Lumasiran (formerly known as ALN-GO1) is an investigational RNAi therapeutic targeting glycolate oxidase (GO) in development for the treatment of Primary Hyperoxaluria Type 1 (PH1). Lumasiran is designed to reduce hepatic levels of the GO enzyme, thereby depleting the substrate necessary for the production of oxalate – the metabolite that directly contributes to the pathophysiology of PH1. Lumasiran utilizes Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. Lumasiran has received both U.S. and EU Orphan Drug Designations, a Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA), and a Priority Medicines (PRIME) designation from the European Medicines Agency (EMA). The safety and efficacy of lumasiran have not been evaluated by the FDA, EMA or any other health authority.

About Primary Hyperoxaluria Type 1 (PH1)
PH1 is an ultra-orphan disease in which excessive oxalate production results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones and nephrocalcinosis. Renal damage is caused by a combination of tubular toxicity from oxalate, calcium oxalate deposition in the kidneys, and urinary obstruction by calcium oxalate stones. Compromised kidney function exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and crystallization in bones, eyes, skin, and heart, leading to severe illness and death. Current treatment options are very limited and include frequent renal dialysis or combined organ transplantation of liver and kidney, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to Vitamin B6 therapy, there are no approved pharmaceutical therapies for PH1.

About RNAi
RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today. Its discovery has been heralded as “a major scientific breakthrough that happens once every decade or so,” and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine. By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function upstream of today’s medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing proteins, thus preventing them from being made. This is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases.

About Alnylam Pharmaceuticals
Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS) diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust discovery platform. Alnylam’s first U.S. FDA-approved RNAi therapeutic is ONPATTRO™ (patisiran) lipid complex injection available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. In the EU, ONPATTRO is approved for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including four product candidates that are in late-stage development. Looking forward, Alnylam will continue to execute on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Alnylam employs over 800 people worldwide and is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam or on LinkedIn.

Alnylam Forward Looking Statements
Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, Alnylam's views with respect to potential for lumasiran to address the significant unmet need that PH1 represents, the initiation of the ILLUMINATE-A Phase 3 study and the expected plans and timing to report topline results from ILLUMINATE-A and, if positive, submit filings for regulatory approval, and expectations regarding "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, Alnylam's ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its product candidates, the pre-clinical and clinical results for its product candidates, which may not be replicated or continue to occur in other subjects or in additional studies or otherwise support further development of product candidates for a specified indication or at all, actions or advice of regulatory agencies, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing, delays, interruptions or failures in the manufacture and supply of its product candidates, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its intellectual property rights against third parties and defend its patent portfolio against challenges from third parties, obtaining and maintaining regulatory approval, pricing and reimbursement for products, progress in establishing a commercial and ex-United States infrastructure, successfully launching, marketing and selling its approved products globally, Alnylam’s ability to successfully expand the indication for ONPATTRO in the future, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage its growth and operating expenses, obtain additional funding to support its business activities, and establish and maintain strategic business alliances and new business initiatives, Alnylam's dependence on third parties for development, manufacture and distribution of products, the outcome of litigation, the risk of government investigations, and unexpected expenditures, as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings that Alnylam makes with the SEC. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Lumasiran has not been approved by the FDA, EMA, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

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